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CLINICAL RESEARCH

Recurrent unexplained syncope may have a cerebral origin: Report of 10 cases of arrhythmogenic epilepsy

Syncope récidivantes inexpliquées d'origine cérébrale : à propos de dix observations d'épilepsie arythmogène

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KEYWORDS

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Summary

Background. — Despite thorough investigation, ~15–20% of syncope cases remain unexplained. An underrecognized cause of syncope may occur when partial epileptic discharges profoundly disrupt normal cardiac rhythm, including cardiac asystole, the so-called arrhythmogenic epilepsy (AE).

Aim. — To report initial results of observations of AE in patients with recurrent, unexplained, traumatic and/or convulsive syncope.

Methods. — Ten patients aged 49 ± 20 years (median 49.5 years; nine women) underwent complete cardiological (including ambulatory Holter electrocardiogram (ECG), echocardiography and head-up tilt test [plus electrophysiology in four patients]) and neurological (including standard electroencephalogram [EEG], computed tomography [CT] and magnetic resonance imaging scan [MRI]) assessments.

Results. — After initial evaluation, neurocardiogenic syncope was suspected in six patients with tilt-induced hypotension \pm bradycardia. Further evaluation (prolonged inpatient video-EEG/ECG monitoring) was undertaken because of non-diagnostic syncope or uncertainty about the diagnosis of neurocardiogenic syncope. While monitored in the neurophysiology lab, a syncopal episode similar to the spontaneous episodes recurred in all 10 patients. Cardiac asystole preceded by partial seizure of temporal onset was documented in nine patients; a

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MOTS CLÉS

Syncope ;
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Traitement
antiépileptique

second-degree atrioventricular (AV) block with a cardiac rhythm of 30 beats per minute preceded by partial seizure of temporal onset was noted in one patient. Eight patients were treated successfully with antiepileptic drugs; two were refractory to antiepileptic therapy and required pacemaker implantation. No patient had recurrent syncope during a median follow-up of 102.5 months (mean 82.2 ± 42 ; range 16–128 months).

Conclusions. — In patients with recurrent, unexplained, traumatic and/or convulsive syncope, AE should be considered as a possible aetiology.

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Résumé

Rappels. — Environ 15 à 20 % des syncopes demeurent inexpliquées malgré un bilan étiologique exhaustif. Des anomalies du rythme cardiaque à type de bradycardie et parfois d'asystole prolongée peuvent survenir lors de crises d'épilepsie partielle. Ces épilepsies arythmogènes pouvant être à l'origine d'authentiques syncopes, sont méconnues et rarement décrites.

Méthodologie et résultats. — Dix patients d'âge moyen 49 ± 20 ans (médiane 49,5 ans, 9F/1H) ayant une histoire de syncopes récidivantes inexpliquées, brutales, traumatiques et/ou convulsivantes ont bénéficié d'un bilan exhaustif cardiologique (Holter ECG de 24 heures, échodoppler cardiaque, test d'inclinaison et étude électrophysiologique endocavitaire chez 4 patients), et neurologique (EEG standard, scanner et IRM cérébrale). Au terme de cette évaluation initiale, une origine neurocardiogénique était suspectée chez six patients chez lesquels le test d'inclinaison a induit une hypotension \pm bradycardie, sans toutefois reproduire les symptômes cliniques. En raison de la sévérité du tableau clinique et de l'absence de certitude diagnostique, un monitoring vidéo-EEG prolongé a été entrepris dans le service de neurophysiologie, en complément du bilan initial. Pendant l'enregistrement vidéo-EEG, une syncope, similaire aux épisodes habituels, est survenue chez chacun des dix patients. Chez neuf patients, une asystole précédée d'une décharge épileptique partielle temporale a été documentée, chez un patient un BAV du deuxième degré Mobitz 2 avec un rythme d'échappement à 30 bpm, également précédé d'une décharge épileptique temporale. Huit patients ont pu être traités efficacement par des médicaments antiépileptiques, et deux patients avec syncopes réfractaires ont été implantés d'un pacemaker. Aucun des dix patients n'a présenté de récurrence de syncope au terme d'un suivi médian de 102,5 mois (moyenne 82.2 ± 42 mois, extrêmes 16 à 28 mois).

Conclusion. — Chez des patients souffrant de syncopes sévères traumatiques et/ou convulsivantes, l'épilepsie arythmogène doit être considérée comme une étiologie possible.

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Background

Syncope is a fairly common medical disorder that accounts for up to 3% of emergency department visits and ~1–6% of hospital admissions [1]. Numerous studies have delineated the multiple potential causes of syncope, which range from benign to life-threatening conditions [2–4]; those that occur most frequently are cardiovascular (neurally-mediated reflex syncope, arrhythmia) or neurological (seizures, transient ischaemic attack). In most cases, the cause is obvious from the clinical picture [5,6]. Clinical findings that suggest a cardiovascular pathophysiology are dizziness or light-headedness before the event and the regaining of consciousness shortly after resuming the supine position, whereas prolonged confusion and myoclonic jerks are suggestive of epilepsy. Patients with cardiovascular syncope may, however, have myoclonic jerks, tonic spasms or urinary incontinence due to transient cerebral hypoperfusion – the so-called convulsive syncope [7]. These patients do not require antiepileptic drugs, but rather need further evaluation and treatment of their cardiovascular disorder. Conversely, patients with partial seizures may have cardiac arrhythmias,

including asystole, which, in turn, can cause syncope – the so-called arrhythmogenic epilepsy (AE) [8–11]. When diagnosed appropriately, these patients may benefit more from antiepileptic medications than from treatment of their arrhythmias, although a pacemaker could be protective for those with asystole whose seizures cannot be controlled.

Cardiac asystole provoked by epileptic seizures is rare [10,11] and only few case reports have been published. Identification of individual patients is challenging because of the therapeutic implications. Indeed, implantation of loop recorders, which provide a symptom-rhythm correlation from a spontaneous episode, is becoming the investigative tool of choice in the setting of recurrent, unexplained syncope [12].

This article reports the initial results of observations of AE in 10 patients referred for evaluation of recurrent, unexplained, traumatic and/or convulsive syncope. All diagnoses were made after documentation of syncope, asystole and electroencephalographic evidence of preceding epileptic activity. These records allowed us to discuss the evidence and consequences of this unusual presentation of unexplained syncope.

Case reports

Initial report, study hypothesis and patient selection

The first, previously reported, case of this series was a 37-year-old woman with no previous medical history, admitted

to hospital for the evaluation of unexplained syncope, sometimes associated with generalized fits [13]. Standard, non-invasive, cardiovascular investigation was non-diagnostic. The head-up tilt test induced a presyncopal episode without reproducing the clinical symptoms. In view of the discordance between tilt test-induced and spontaneous symptoms, a neurological point of view was requested. During

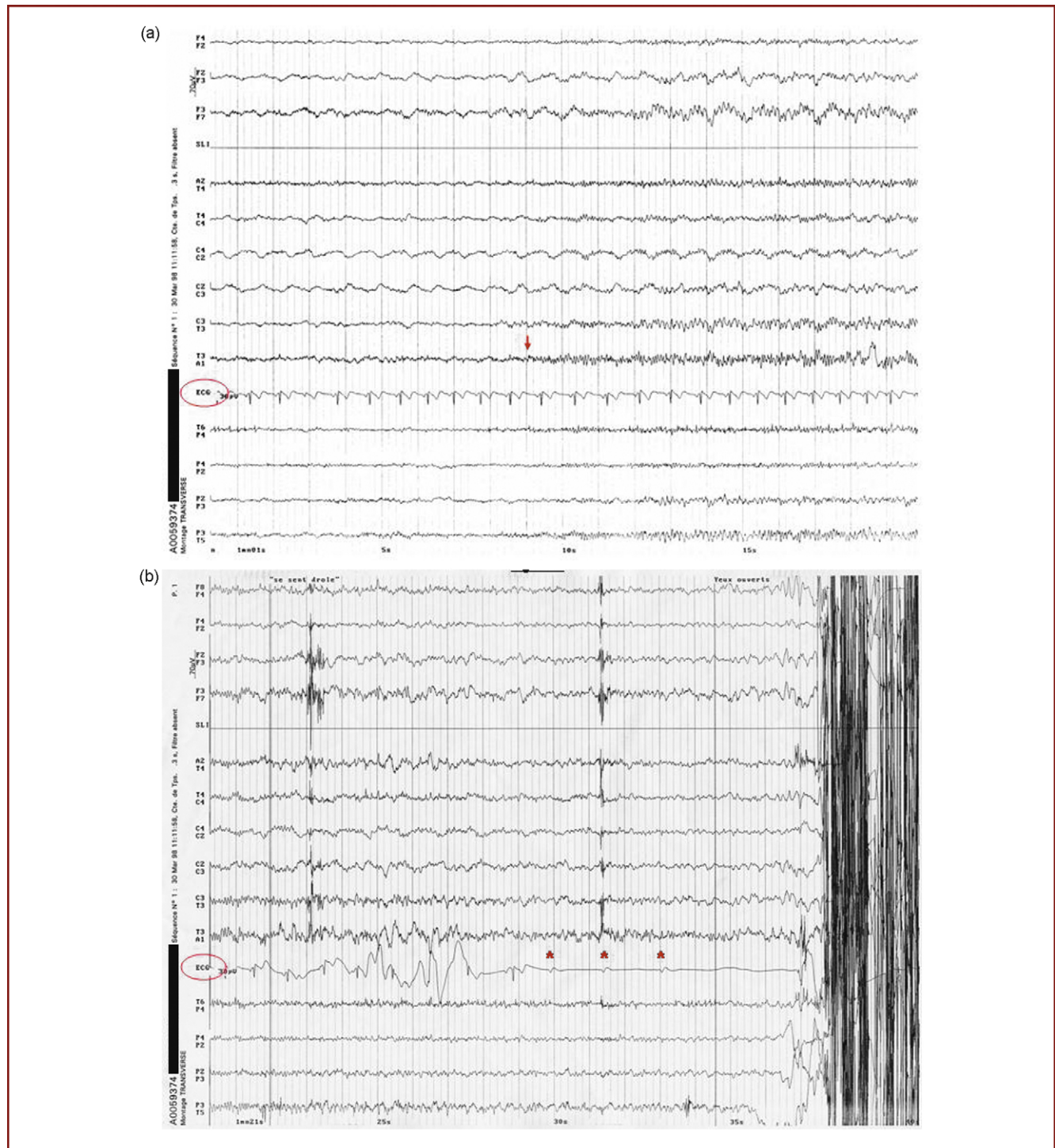


Figure 1. Simultaneous EEG/ECG recording in patient #1. a: ↓ partial seizure onset with only electrical abnormalities; the patient is asymptomatic. Recording of spike waves over the left centrottemporal region. The ECG channel shows sinus tachycardia at 120 beats per minute; b: sinus arrest after complete AV block complicated by generalized epilepsy reproducing the clinical symptoms.

prolonged video-electroencephalogram/electrocardiogram (EEG/ECG) recording, syncope complete atrioventricular (AV) block occurred, reproducing exactly the same clinical symptoms. Analysis of the sequence of events showed that the conduction defect had arisen after the onset of the epileptic fit (Fig. 1). The patient was treated successfully with antiepileptic drugs and remained asymptomatic.

Based on this initial experience, although syncope is defined as a transient, self-limited loss of consciousness with spontaneous recovery, we hypothesized that AE might be a possible aetiology. Considering this, patients admitted to our syncope clinic with both recurrent, unexplained, severe, traumatic and/or convulsive syncope that justified the need for a precise diagnosis and specific therapy, and unsuccessful and/or inconclusive cardiovascular investigation were always referred to the neurophysiology department.

From 1999 until February 2007, nine new observations were documented, leading to a total of 10 reports of AE. During the same period, 131 undiagnosed patients were referred to the neurophysiology lab (out of approximately 4500 patients evaluated in our syncope unit).

Clinical presentation and baseline characteristics of the study population

Patients and witnesses underwent careful interrogation regarding symptom burden, provocative situations, perisyncope symptoms and relevant medical history. The AE patients were aged 49.3 ± 20 years (median 49.5 years), were predominantly women and presented with a history of multiple episodes of abrupt loss of consciousness (median 8) for which no prodrome was reported. Witnesses reported that the patients appeared completely normal until they suddenly lost consciousness; they did not look pale and did not turn cyanotic. In patients #3, #4 and #6, a possible history of 'black-outs' lasting inferior to 1 min was noted and patient #7 mentioned a possible history of hallucinations and oral automatisms. Patient #9 reported transitory aphasia (< 30 min) only after their last recurrent syncope. Patients #2, #8 and #9 had a history of mild hypertension; the others had no cardiac disease.

Initial cardiovascular and neurological evaluation

All patients had a normal physical examination, 12-lead ECG and echocardiography. A 24-hour Holter ECG documented an asymptomatic, brief (< 30 s) episode of second-degree type 2 AV block in patient #9. Despite the absence of classical triggers, vasovagal syncope was hypothesized and the head-up tilt test was performed according to a protocol described previously [14]. Reproduction of symptoms associated with the patient's clinical event was required to define a positive test. The tilt test elicited symptomatic hypotension \pm bradycardia in five patients (during the passive phase in patient #5 and the provocative phase in patients #1, #2, #4 and #6). Patient #7 had a sudden, brief (< 30 s) loss of tone with normal haemodynamic parameters. None of the induced symptoms, however, reproduced the clinical symptoms and the tilt test results were considered to be false positive. Invasive electrophysiological studies, performed

earlier in our management of four of the patients, were normal. Neurological examination, baseline EEG (except in patient #9) and computed tomography (CT) brain scan were normal. Table 1 summarizes the characteristics of the study patients.

Neurophysiological evaluation and inpatient video-EEG methodology

All ten patients were investigated with simultaneous long ECG and EEG recordings, and magnetic resonance imaging (MRI) brain scans in the neurophysiology lab. Inpatient video-EEG/ECG recording was carried out within 48 h to 5 days of the initial assessment. Standard EEG and ECG recording equipment was used, with an additional digital video camera. EEG monitoring was performed by using surface electrodes placing according to the international 10–20 system, with additional T₁/T₂ or sphenoidal electrodes and two electrodes for continuous ECG co-registration [15]. Comprehensive electrophysiological information obtained from continuous video-EEG/ECG recordings was analysed.

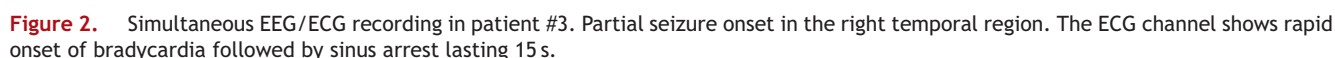
Ictal EEG activity was evaluated for lateralization, onset, progression and distribution, to correlate this information with the onset, duration and type of the co-registered asystolic event, and with semiologic phenomena observed in the split-screen video monitoring. ECG analysis was done independently by a cardiologist and the EEGs were analysed by an epileptologist.

ECG and EEG correlates during the event, and therapeutic approach

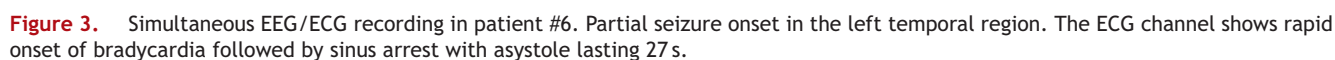
In all ten patients, prolonged EEG/ECG monitoring captured unprovoked or provoked partial seizures. Ictal EEG changes always preceded the clinical onset. Patients #2, #4 and #6 reported auditory hallucinations and complained of a strange unease associated with visceral symptoms of nausea and warmth. A left (patients #1, #4–#7, #9 and #10) or right (patients #2, #3 and #8) temporal EEG discharge activity of increasing amplitude and rate was recorded. Within ~5–10 s of seizure onset, an abrupt, short period of bradycardia was followed by prolonged asystole lasting 10–40 s, related to complete AV block followed by sinus arrest in patient #1 (Fig. 1) and sinus arrest in patients #2–#8 and #10 (Figs. 2–4), during which all had syncope with bilateral tonic spasms and generalized epilepsy, sometimes accompanied with suppression of the EEG. A second degree AV block with a cardiac rhythm of 30 beats per minute was documented in patient #9. Consciousness was restored after the heart rhythm returned to normal. Post-ictal disorientation was not prominent. These ictal EEG changes differ significantly from those recorded in patients undergoing a combined EEG/tilt test for the evaluation of convulsive syncope (Fig. 5). MRI brain scans were always normal except in patient #2, in whom posttraumatic sequelae were noted. Patients therefore fulfilled the criteria for the diagnosis of AE and were treated subsequently with various combinations of antiepileptic drugs. Table 2 summarizes the ictal cardiac manifestations of the study patients.

Patient	Sex (age)	Syncope duration (yrs)	No. of syncopes	Trauma/injury/convulsion	Baseline ECG	Holter ECG	TTE	60° head-up tilt test	EP study	Standard EEG
1	F (37)	4	20	Yes/Yes/Yes	Normal	Normal	Normal	Hypotension	—	Normal
2	F (77)	5	3	Yes/Yes/Yes	1st degree AV block	Normal	Normal	Hypotension + bradycardia	Normal	Normal
3	F (47)	2	20	Yes/Yes/Yes	Normal	Normal	Normal	Normal	Normal	Normal
4	F (54)	8	14	Yes/No/No	Normal	Normal	Normal	Hypotension	Normal	Normal
5	M (52)	1	3	Yes/No/No	Normal	Normal	Normal	Hypotension + bradycardia	Normal	Normal
6	F (21)	2	10	Yes/Yes/Yes	Normal	Normal	Normal	Hypotension	—	Normal
7	F (29)	18	5	Yes/Yes/No	Normal	Normal	Normal	Loss of postural tone with normal HR and BP	—	Normal
8	F (83)	3	6	Yes/No/No	Normal	Normal	Normal	Normal	—	Normal
9	F (59)	2	8	Yes/Yes/No	Incomplete RBBB	Paroxysmal 2nd degree AVB	Normal	—	—	Left TE discharges
10	F (34)	0	8	Yes/Yes/Yes	Normal	Normal	Normal	—	—	Normal

AV: atrioventricular; BP: blood pressure; ECG: electrocardiogram; EEG: electroencephalogram; EP: electrophysiological; F: female; HR: heart rate; M: male; RBBB: right bundle branch block; TE: temporal epileptic; TTE: transthoracic echocardiography.



maintained on adjusted doses of antiepileptic drugs. After implantation, they had no further recurrence, although patient #3 complained of brief episodes of absence lasting < 30 s. Antiepileptic drugs were the treatment of choice for the other eight patients. After a median follow-up of



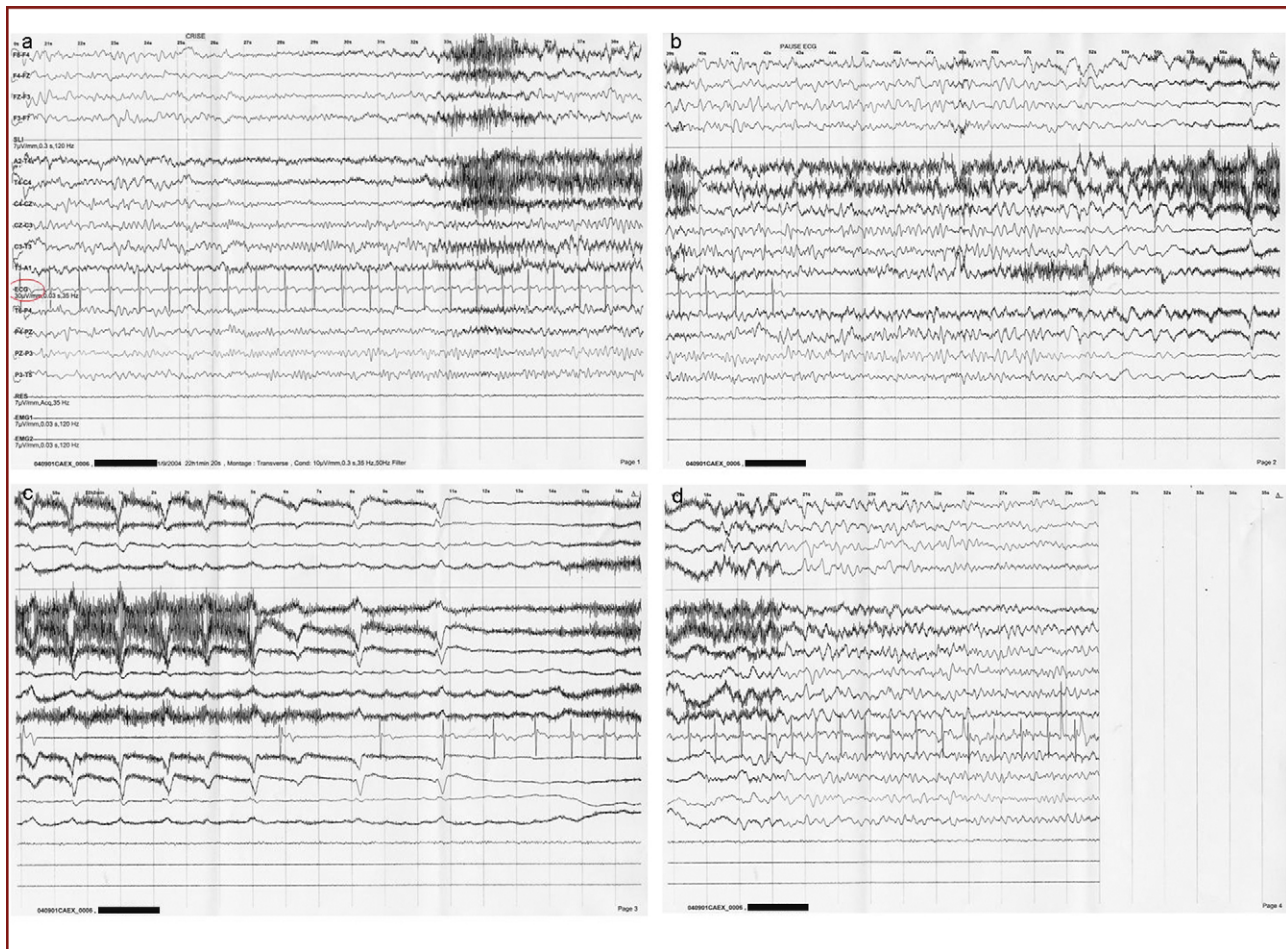


Figure 4. Simultaneous EEG/ECG recording in patient #8. a: partial seizure onset in the right temporal region. The ECG channel shows a normal sinus rhythm at 90 beats per minute. The patient is asymptomatic; b: continuous ECG recording showing cardiac asystole; c: secondarily generalized tonic-clonic seizures; d: end of episode.

102.5 months (mean 82 ± 42 , range 16–128 months), all 10 patients remained asymptomatic (Table 2).

Discussion

Dysfunction of heart or brain may cause syncope. Both organs are functionally interdependent, which explains the diagnostic difficulties sometimes encountered in clinical practice. For instance, cardiac arrhythmias may lead to decreased circulation to the brain, which can manifest itself as syncope, sometimes with seizures of the myoclonic type. Conversely, alteration of the heart rate during a seizure is a well-known phenomenon, and partial epilepsy can induce bradyarrhythmias and syncope. Therefore, the medical practitioner may easily confuse AE with an authentic cardiac arrhythmia, thus delaying the appropriate diagnosis and therapy. This unusual manifestation of syncope is understood poorly in terms of both its pathophysiological characteristics and prevalence. To the best of our knowledge, we are the first to employ simultaneous video-EEG/ECG in the description of this unusual presentation of recurrent, unexplained syncope.

Since Russell's observation in 1906 of the cessation of the pulse during a seizure [16], many clinical and experimental studies have shown that cardiac rhythm changes may occur during focal epileptic seizures [8,17–23]. This applies particularly to the anterior hypothalamus and the insular cortex, where stimulation may induce sinus bradycardia and even sinus arrest, with the impulses being transmitted to the heart via the dorsal vagal motor nucleus and the vagal nerve. With greater use of simultaneous EEG/ECG recording, such changes have been subjected to further study. The term AE was used by Pritchett et al. in 1980 [22] and then by Gilchrist in 1985 [17] to report a cardiac arrhythmia with a cerebral origin. Bradyarrhythmias, however, have been reported only rarely in conjunction with partial epilepsy [8,9,23]. Our patients had clinically significant cardiac arrhythmias, despite the absence of a cardiac history, and a normal cardiovascular assessment. In five of eight of the patients, tilt testing elicited hypotension and/or bradycardia, which is probably indicative of a susceptibility to parasympathetic autonomic dysfunction [14]. When compared with patients on whom we have reported previously, who had tilt-test induced asystole, the AE patients were older (49 ± 20 versus 24 ± 15 years, respectively) and had a more severe clinical

Table 2 Recorded ictal cardiac manifestations during prolonged video-EEG/ECG monitoring of unprovoked or provoked seizures in the neurophysiology lab.

Patient	EEG localization	Peri-ictal heart rhythm	Mechanisms	Cause of epilepsy	Treatment	Follow-up (months)	Syncope recurrence
1	Left TLE	30-second asystole	Complete AV block	Cryptogenic	Vigabatrin + carbamazepine	128	No
2	Right TLE	10-second asystole	Sinus arrest	Posttraumatic	Carbamazepine	124	No
3	Right TLE	30-second asystole	Sinus arrest	Cryptogenic	Vigabatrin + PM	111	No
4	Left TLE	15-second asystole	Sinus arrest	Cryptogenic	Oxcarbazepine + clobazam	110	No
5	Left TLE	30-second asystole	Sinus arrest	Cryptogenic	Carbamazepine	105	No
6	Left TLE	27-second asystole	Sinus arrest	Cryptogenic	Carbamazepine + topiramate + PM	100	No (since PM)
7	Left TLE	12-second asystole	Sinus arrest	Cryptogenic	Lamotrigine	53	No
8	Right TLE	20-second asystole	Sinus arrest	Cryptogenic	Oxcarbazepine	51	No
9	Left TLE	Bradycardia 30 bpm	2nd degree AV block	Cryptogenic	Lamotrigine	24	No
10	Left TLE	40-second asystole	Sinus arrest	Left hippocampic sclerosis	Carbamazepine + levetiracetam	16	1 syncope during AED titration

AED: antiepileptic drug; AV: atrioventricular; bpm: beats per minute; EEG: electroencephalogram; PM: pacemaker; TLE: temporal lobe epilepsy.

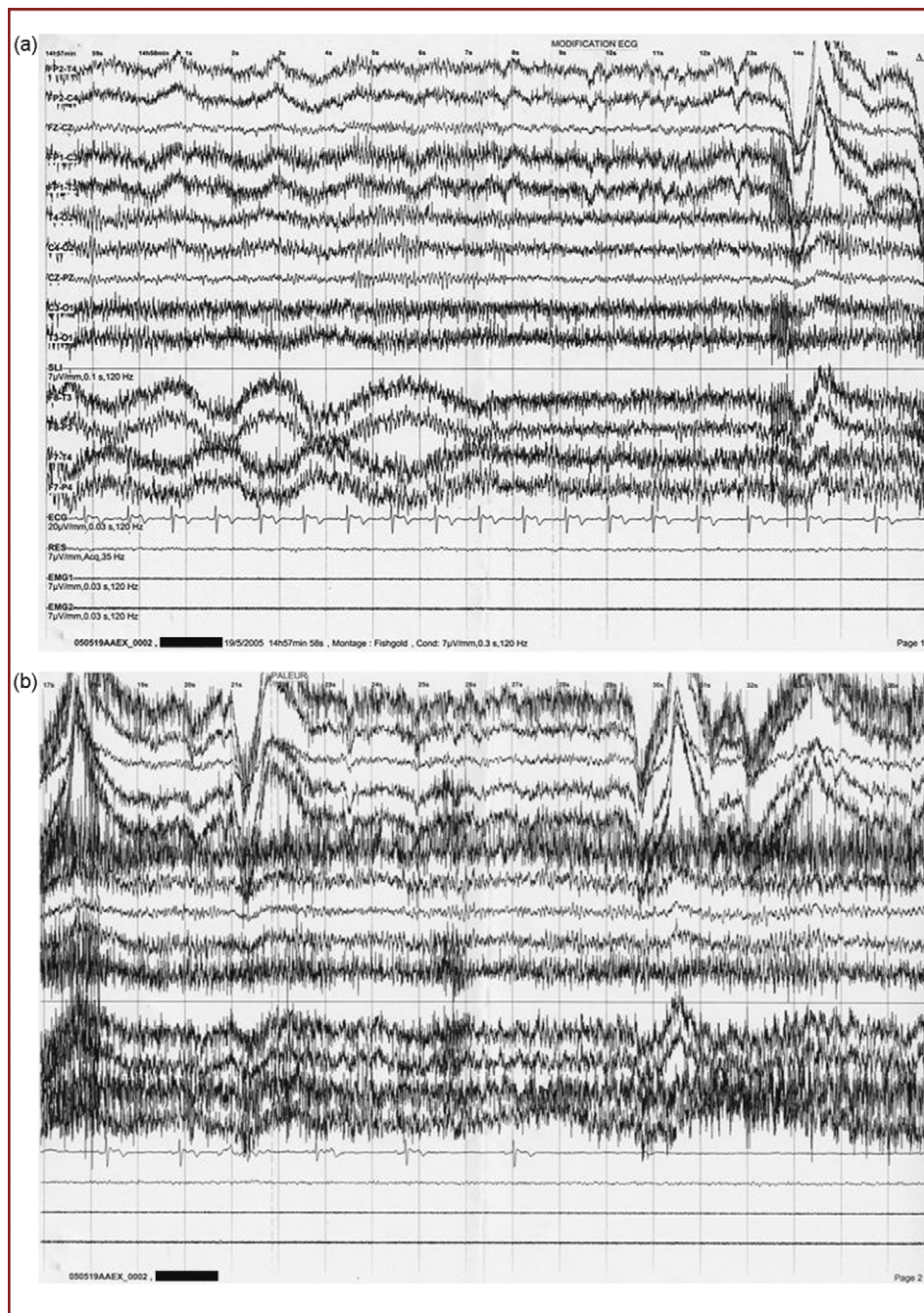


Figure 5. Simultaneous EEG/ECG recording during tilt test in a patient evaluated for convulsive syncope typically showing no evidence of seizure, but rather progressive slowing progressing to flattening – a sequence typical of cerebral hypoperfusion. *Please note that this example is not one of the patients in the study and is provided only for comparison with the AE patients.* a: the ECG channel shows a progressive bradycardia; b: the ECG channel shows a progressive bradycardia followed by sinus arrest with asystole lasting 17s with secondarily generalized tonic-clonic seizures.

presentation (mean asystole duration 24 ± 9 versus 12 ± 5 s, respectively) [24]. It is likely that parasympathetic influences mediated the asystole described in our predisposed patients, and probably that described in earlier reports. The hypothesis is that in predisposed patients, partial epileptic discharge triggers vagal discharge, leading to cardioinhibitory, neurally mediated syncope, which, in turn, triggers a generalized convulsion. Therefore, ‘asymptomatic or paucisymptomatic’ partial epileptic patients may be referred

for unexplained ‘syncope’ rather than for seizure-like symptoms.

Evidence for cerebral localization of cardiovascular autonomic control is growing. In both animal models and humans, stimulation and recording studies implicate the amygdala in the control of heart rate and blood pressure. The amygdala receives both direct and indirect projections from the autonomic nervous system afferents and also projects into hypothalamus and brainstem centres for autonomic nervous

system homeostasis. Thus, seizures that have their foci in the temporal lobe may propagate easily through these centres. Human cortical stimulation studies have shown that the left hemisphere – particularly the insula – could be important in the generation of parasympathetic cardiac effects, and the right hemisphere is implicated potentially in the regulation of sympathetic function. Oppenheimer et al. reported bradycardia and depressor responses during stimulation of the left anterior insula [19]. The converse applied for right insular stimulation. The many interconnections between the insular cortex, limbic system and hypothalamus led the authors to speculate that this region might represent the centre of cortical arrhythmogenesis. The hemispheric asymmetry is also supported by described changes in heart rate and heart rate variability during the intracarotid sodium amytal test [25] and electroconvulsive therapy [26], and by decreased heart rate following right-sided, intracarotid, amobarbital injection and increased heart rate following left-sided, intracarotid, amobarbital injection [27].

In our study, all patients had temporal lobe epilepsy, consistent with findings from previous reports [8,9,28]. No strong lateralization was observed; however, seven patients had left temporal onset and three had right temporal onset. Although some authors have found lateralization of the cardiac effects of insular cortex stimulation in humans, our personal observations, as well as the review of the literature [8,9,28], do not support the view that similar lateralized differences are present in the AE. However, the proportion of cases of AE with temporal lobe epilepsy must be viewed in light of the fact that more than 60% of patients with epilepsy have partial seizures, most of which arise from the temporal lobe, and it remains uncertain whether our 'syncope' patients reflect bias of selection. In our study, women were more often affected by AE, which contrasts with the findings of Reeves et al., who observed an approximate 5:1 ratio of men to women [28]; whether this reflects bias of selection is also uncertain.

There are two groups in which the diagnosis of AE is likely to be missed. The group reported most frequently comprises patients who are known to have partial epilepsy, but in whom episodic loss of consciousness may be attributed only to the cerebral effects of seizures. The group reported less frequently comprises patients in whom syncope may be attributed to an intrinsic cardiac disease, without appreciation that cardiac dysfunction may be the result of a seizure. This distinction is of more than academic interest, as Holter ECG monitoring alone lacks the essential EEG component in the diagnosis of AE. In our present study, the clinical episodes were not typical of generalized epileptic seizures and the usual symptoms and signs of partial seizures were not revealed prominently. Prolonged postictal obnubulation was not present. The normal findings on the neurological examination, standard EEG and CT brain scan also made a primary diagnosis of epilepsy unlikely. Patients were referred to our centre because they seemed to present with syncope clinically. They usually present with severe symptoms including trauma and injury due to the absence of prodrome and cardio-inhibitory reflex, and were referred to the neurophysiology lab after unsuccessful cardiovascular investigation, only based on this criterion. In some reports, a pacemaker was implanted before realization that the patient's difficulties stemmed from epilepsy

[28,29]. We can speculate that cardiac pacing may not be appropriate first-line therapy in the setting of asystole secondary to AE. This supports the conclusion, based on our median follow-up of 102.5 months, that such a disorder can be managed successfully with antiepileptic drugs alone; only a few patients with refractory AE may require dual therapy of antiepileptic drugs and a pacemaker. Although costly, prolonged in-patient video-EEG/ECG monitoring provides a better method of evaluating problematic syncope and should be considered earlier after non-diagnostic standard cardiovascular investigation in patients experiencing severe, recurrent, traumatic syncopal episodes.

Conclusions

The frequency of AE is unknown and its role in recurrent unexplained syncope remains to be confirmed. Our study is small, consisting of 10 patients. Thus, any conclusion drawn from our data must be considered in this context. However, our study has shown that in patients evaluated in the setting of recurrent, unexplained, traumatic and/or convulsive syncope, AE should be considered as a possible aetiology and prolonged video-EEG/ECG monitoring provides the best method for differentiating AE from other diagnoses.

Conflicts of interests

None declared.

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